Applicants expressly reserve the right to pursue without prejudice the originally filed claims as well as other disclosed subject matter at a latter date. Applicants further gratefully acknowledge that certain rejections raised in the previous Office Action dated December 26 have not been raised again in this Action and thus are presumed to have been overcome by Applicant's traversal provided in their previous response. In particular, rejections not raised in the most recent Office Action and presumed overcome include the previously-raised rejection under 35 U.S.C. 102(e) in view of Truong et al., U.S. Patent No. 6,025337 and rejections under 35 U.S.C. 103 in view of: Truong et al. and Beer et al. ((1997) Adv. Drug Deliver Review 27: 59-66); as well as Truong et al. and Casey et al. ((1991) Oncogene 6: 1791-7); Truong et al. and Beer et al. further in view of Leong et al. (U.S. Patent No. 5,759,582); and Truong et al., Beer et al., and Leong et al. further in view of Watts et al. (WO 98/30207).

REJECTIONS

Rejections Under 35 U.S.C. §112, first paragraph- Enablement

The Office Action states that claims 32, 34, 39, 17-20 and 22 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection.

The Office Action states that "Regarding to the gene therapy aspect of the claims, the specification is not enabled for the claimed invention because it fails to provide guidance for one skilled in the art on how to make and use the claimed methods and composition to obtain any therapeutic effect contemplated by Applicants to treat a plethora of diseases, disorders or genetic defects such as Duchenne and Becker muscular dystrophy, adenosine deaminase deficiency, cancer, Parkinson's, Alzheimer's (and) AIDS among others..." In particular, the Office Action states that "there is no specific guidance as to promoters, vectors or dosages that are utilized to treat a particular disease, disorder or a genetic defect." Applicants note that, notwithstanding the disputed matter regarding whether gene therapeutic applications of the invention are fully

enabled in the art, the ability to cure the listed disorders with gene therapy and the identity of vectors for achieving this result are not determinative of enablement of the instant claimed invention as discussed in detail below.

First, Applicants note that the Office Action apparently rejects Applicants' assertion that gene therapeutic applications of the claimed invention are credible given existing know-how at the time of invention when it states that the "Examiner respectfully finds Applicants' argument to be unpersuasive because the above rejection is not made for the lack of utility, but rather for the lack of enablement." Nonetheless, it is relevant to point out that the interrelatedness of the utility and enablement (make and use) requirements has been addressed in *In re Bran*. 51 F.3d 1560 (Fed. Cir. 1995). In *Brana*, the court found that, despite the PTO's assertions that the applicants' anti-tumor compounds were not credible, that applicants had fully complied with the enablement requirement. The court emphasized that properly patented pharmaceutical inventions usually require further research and development. Thus, the point at which an invention becomes useful enough for a patent will often be long before it is ready for human use. To hold otherwise, the court noted, would raise the costs of obtaining patent protection for new inventions and remove the incentive to fully research and develop vital drugs and potential cures. *Id.* at 1567-8. Accordingly, existing law supports Applicants' assertions that sufficient advancement in the technology of gene therapy existed at the time of filing to support enablement of even gene therapeutic applications of the claimed invention.

Furthermore, notwithstanding Applicants' disagreement with the assertion presented in the Office Action that gene therapeutic applications of the instant invention were "unpredictable" and therefore not fully enabled by the present application at the time of filing, Applicants respectfully note that enablement of gene therapy methods is not determinative of the patentability of the invention in this case. Notably, although courts have often set a higher standard of disclosure to method of treatment claims,[1] this does not apply to a composition of matter claim that is otherwise enabled by the teachings of the application. Indeed rejected claims 17-20 and 22 are drawn to a composition for controlled release of a nucleic acid, and these

[1] The higher standard grounded in the notion that whereas compound claims do not contain a statement of utility -- and as such, any showing of utility will suffice -- by contrast, corresponding claims drawn to methods of treating a disease or condition must be judged relative to the stated utility and not just any demonstration of utility.

compositions have uses supported by the application that are independent of gene therapeutic applications including delivery of a toxin for killing undesirable cells (see, e.g., page 40, line 7); for DNA vaccination (see, e.g., page 3, lines 17-21); for imaging (see e.g. page 22, lines 11-26) and for transformation of cells in vitro for *ex vivo* gene therapy applications (see e.g. page 38, lines 13 to 15). The requirements of 35 U.S.C. § 112, first paragraph (enablement) do not include a showing that all conceivable uses of this claimed composition be enabled. Rather, a claimed composition is enabled, when an Applicants show how to make and use the claimed composition. To rule otherwise would lead to the perverse legal result that composition claims in biotechnology-related arts are never patentable inasmuch as new biotechnological applications of such compositions, not enabled or even evident from the current state of the art, are likely to be developed and would potentially infringe claims to the biotechnical compositions of which they make use. This is simply not the state of existing patent law.[2] In the instant case, Applicants have supported numerous uses of the claimed invention. The Office Action has not fully addressed these valid uses of the claimed invention. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

The Office Action further states that claims 1-2, 4-10, 13-16, 21, 23-31, 33, 35, and 40-49 have been rejected under 35 U.S.C. § 112, first paragraph for allegedly failing to enable "other embodiments of the claims." In particular, the Office Action states that "since the arrangement of the critical elements of the claimed composition is not clearly defined, it is uncertain whether any and all compositions having the recited components would function properly in releasing a nucleic acid molecule in a contol(led) and sustained manner for effectively delivering the nucleic acid into a cell." The Office Action further states that "the state of the art and the present application and the instant specification only teach that polycations such as albumin, collagen, elastin, gelatin, and polyanions such as chondroitin sulfate, dermatin sulfate, hyaluronic acid (and) heparin may be used to form the coacervate microsphere or microcapsule." Applicants respectfully traverse this rejection, and each of these bases for this rejection, for the reasons that follow.

---

[2] In a simpler example in the mechanical arts, this would lead to the perverse conclusion that a claim to a new bolt, supported by a description of a manner of making and using the bolt in Machine X - presently known in the art, is not enabled inasmuch as the same bolt might be used in Machine Y- which has yet to be developed.

First, to the extent that the basis of this rejection is the alleged "uncertain(ty)" of the operability of the invention, Applicants note that a *prima facie* case for lack of enablement requires that the Examiner set forth evidence or technical reasoning substantiating the basis for the asserted doubts. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1994) and MPEP § 2164.04. Applicants respectfully state that adequate evidence or technical reasoning substantiating the basis for rejection is lacking in this case. In particular, the basis of the statement "it is also well known in the art that many polycations.....e.g. serum albumin" do not form the subject coacervates is unclear. Indeed, while Truong et al. (U.S. Patent No. 6,025,337 at col. 3, lines 27-34) is cited in the Office Action for the proposition that "polylysine is the only alternative polycation....capable of complexing with nucleic acid to form microparticles," a careful reading of the cited material indicates that it provides no such technical support to the rejection (stating only that "Poly-L-Lysine may be particularly useful as the polymeric cation of the present invention" ('337 at col. 3, lines 3-34)).

Furthermore, there is support in the art for the proposition that any number of different combinations of anionic and cationic polymers are capable of forming complex coacervates that effective for delivery to mammalian cells (see e.g. Matthew et al. (1993) Biotechnol Prog 9: 510-9 (in which several tested polyanion/polycation combinations had properties superior to those of alginate-polylysine). In particular, several studies support the use of serum albumin in forming certain coacervate/microspheres (see e.g. Kaibara et al. (2000) Biomacromolecules 1: 100-7; and Burgess and Singh (1993) J Pharm Pharmacol 45: 586-91). Accordingly, the Office Action fails to provide a sufficient basis in evidence or technical reasoning sufficient to support the rejection and reconsideration and removal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. §112, second paragraph- Indefiniteness

The Office Action states that claims 1-28, 30, 34, 35, 40-41, 43, 46 and 49 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly failing to particularly point out and distinctly claim the subject matter which the applicant regards as his invention. Applicants respectfully traverse this rejection to the extent that it is maintained over the claims as amended.

Regarding claim 1, the Office Action states that claim 1 and its dependent claims are unclear because "it is unclear what is the structural relationship between component b) a nucleic

acid and component c) a delivery agent in the claimed composition." In particular the Examiner has inquired as to whether these components are "structurally linked or do they interact in any manner in the composition?" Applicants respectfully point out that the need to further describe a "structural relationship" between the components is not clear provided the enabling description found in the specification and the standard use of the open-term "comprising" in the relevant claims. Indeed, the application is replete with teachings regarding the nature of the subject "delivery agents" of the invention and their potential relationship to the other components. For example, the delivery agent may be a sterol or lipid (see, e.g., the application at page 5, lines 15-17), or a virus particle (see, e.g., the application at page 5, lines 3-14) or any of a variety of amphiphilic compounds that may be included in the formulation (see, e.g., the application at page 31, lines 21-33) that is included in the coacervate formulation. In other embodiments, the agent is an antibody or cell surface ligand which may be cross-linked with a gene binding agent such as poly-lysine (see, e.g., the application at page 32, lines 1-12). Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

The Office Action states that the recitation "said viral vector" appearing in claim 24 lacks sufficient antecedent basis. Accordingly Applicants have amended claim 24 to recite "a viral vector," thereby obviating this grounds for rejection. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

The Office Action states that the recitation "the cells" appearing in claim 32 lacks sufficient antecedent basis. Accordingly, Applicants have amended claim 32 to recite "the cell," along with other consistent grammatical changes indicating sufficiency of a singular cell, thereby obviating this grounds for rejection. Applicants note that appropriate antecedent basis for a single cell (i.e. "the cell") appears in claim 30 (line 1), from which claim 32 depends. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

The Office Action states that the recitation "administering to said host" appearing in claim 34 lacks sufficient antecedent basis. Accordingly Applicants have amended claim 34 to recite "to a host," thereby obviating this grounds for rejection. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

The Office Action states that the phrase "instructions for using" appearing in claim 35 is unclear. Applicants respectfully point out that support for "kits" of the invention and supporting "instructions for using the kit" are supported in the application (see, e.g., page 5, lines 26-30). Furthermore the use of the phrase "instructions for using the kit" is widely used (see, e.g., recently-issued U.S. Patent Nos. 6,365,729, 6,365,417 and 6,362,164). Accordingly, Applicants assert that the subject claim is not indefinite and reconsideration and withdrawal of the rejection is respectfully requested.

Finally, the Office Action alleges that claims 40-41, 43 and 46 are unclear for lack of a "structural relationship between the delivery agent and the nucleic acid." This issue was addressed in the response to rejection of claim 1 under 35 U.S.C. § 112, second paragraph, which appears above. Applicants reiterate these grounds for traversal and respectfully request reconsideration and withdrawal of this rejection.

Rejections Under 35 U.S.C. §102(e)

The Office Action states that claims 1-2, 10 and 29 have been rejected under 35 U.S.C. § 102(e) as being anticipated by Russell-Jones, et al. (U.S. Patent No. 6,159,502). In particular, the Office Action states that the Russell-Jones et al. patent teaches microsphere coacervates composed of polyanions with polycations, as well as the use of microspheres to deliver DNA or RNA, and, still further that "a coacervate comprising a polyanion and a polylysine (also a delivery agent) that encapsulates a DNA or RNA or ribozyme (is) taught by Russell-Jones" (emphasis added).

Not in acquiescence to this rejection, but in order to expedite prosecution of the application, Applicants have amended claims 1 and 29 so as to clarify that the "delivery agent" component of the invention is other that the cationic molecule of the coacervate. Applicants believe these amendments effectively obviate this rejection and, accordingly, reconsideration and withdrawal of this rejection is respectfully requested. Applicants further respectfully indicate that none of such amendments are intended to narrow, or cause a narrowing of, the scope of any of the pending claims. Finally, Applicants note that they expressly reserve the right to pursue without prejudice the originally filed claims as well as other disclosed subject matter at a latter date.

Rejections Under 35 U.S.C. §103

The Office Action still further states that claims 1-2, 4-5, 11-20, 23-32, 33-39 and 48 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Russell-Jones et al. (U.S. Patent No. 6,159,502) in view of Beer et al. ((1997) Adv. Drug Delivery Review 27: 59-65). Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Applicants note that the above-directed amendments to claim 1 and 29 warrant reconsideration and withdrawal of this rejection. These clarifying amendments further serve to distinguish the instant invention from the cited art. Furthermore, Applicants note that the asserted combination of Russell-Jones et al. with Beer et al. suffers from the defects of record noted in the response to the previous Office Action in which Truong et al. (U.S. Patent No. 6,025,337) in view of Beer et al. was cited under 35 U.S.C. § 103(a). Accordingly, reconsideration and withdrawal of the rejection of claims 1-2, 4-5, 11-20, 23-32, 33-39 and 48 under 35 U.S.C. § 103(a) as unpatentable over Russell-Jones et al. in view of Beer et al. is respectfully requested.

The Office Action further states that claims 40-47 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Russell-Jones et al. (U.S. Patent No. 6,159,502) in view of Beer et al. ((1997) Adv. Drug Delivery Review 27: 59-65) and further in view of Leong et al. (U.S. Patent No. 5,759,582). Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Applicants note that the clarifying amendments made to claims 1 and 29 are unnecessary in the case of subject independent claim 40 where the independent nature of the "cationic molecule" and the "delivery agent" is clear. Furthermore, Applicants note that the asserted combination of Russell-Jones et al. with Beer et al. and Leong et al. suffers from the defects of record noted in the response to the previous Office Action in which claims 40-47 were rejected under under 35 U.S.C. § 103(a) as being unpatentable over Leong et al. in view of Truong et al. and Beer et al.. Accordingly, reconsideration and withdrawal of the rejection of claims 40-47 under 35 U.S.C. § 103(a) as being unpatentable over Russell-Jones et al. in view of Beer et al. and Leong et al. is respectfully requested.

The Office Action further states that claims 1-6, 11-15, 17, 22 and 49 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Russell-Jones et al. (U.S. Patent No. 6,159,502) in view of McElligot et al. (WO 94/23738). Finally, the Office Action also states that claims 1, 2 and 7-9 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the Russell-Jones et al. and McElligot et al. combination of references further in view of Gombotz et al. (U.S. Patent No. 5,942,253). Applicants respectfully traverse these rejections to the extent they are maintained over the claims as amended.

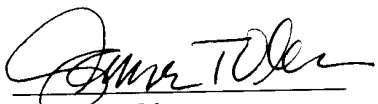
Applicants note that the above-directed amendments warrant reconsideration and withdrawal of this rejection. These clarifying amendments further serve to distinguish the instant invention from the cited art. Furthermore, Applicants note that the asserted combination of Russell-Jones et al. with McElligot et al. suffers from several of the defects of record in the art cited under 35 U.S.C. § 103(a) as noted in the response to the previous Office Action. Still further, Applicants note that McElligot et al. repeatedly recites the feature that the nucleic acid be conjugated to the "promoting material" "by way of chemical bonds....which promotes the uptake or the transport..." (McElligot et al. at page 5, lines 16-18, emphasis added). Accordingly, the teachings of McElligot et al. would lead the skilled artisan away from making substitutions of these essential features with the microsphere formulations of Russell-Jones et al.. Therefore the teachings of McElligot et al. would lead the skilled artisan away making the claimed invention. Accordingly, reconsideration and withdrawal of the rejection of claims 1-6, 11-15, 17, 22 and 49 under 35 U.S.C. § 103(a) as unpatentable over Russell-Jones et al. in view of McElligot et al. as well as of claims 1-2 and 7-9 in view of Russell-Jones et al./McElligot et al. further in view of Gombotz et al. is respectfully requested.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims now pending are in condition for allowance, and notification of such is respectfully requested. If for any reason a telephonic conference with the Applicant would be helpful in expediting prosecution of the instant application, the Examiner is invited to call the undersigned at (617) 832-1000.

If there are any other fees due in connection with the filing of this Response, please charge the fees to our Deposit Account No. 06-1448.

Respectfully submitted,
FOLEY, HOAG, & ELIOT



James T. Olesen
Reg. No. 46,967
Agent for Applicants

April 3, 2002

Customer No.: 25181
Patent Group
Foley, Hoag & Eliot LLP
One Post Office Square
Boston, MA 02109-2170
Telephone: (617) 832-1000
Facsimile: (617) 832-7000

Marked-Up Copy of the Amended Claims with Changes Shown Thereon

1. **(Twice Amended)** A composition for controlled release of a nucleic acid, comprising:

a. a coacervate;

b. a nucleic acid incorporated in said coacervate; and

c. a delivery agent incorporated in said coacervate,

wherein the coacervate comprises a cationic molecule and an anionic molecule other than said nucleic acid and the delivery agent is other than said cationic molecule of the coacervate.

2. The composition of claim 1, wherein said coacervate is a microsphere.

4. The composition of claim 2, wherein said nucleic acid is a transfer vector.

5. The composition of claim 4, wherein said transfer vector includes a transgene.

6. The composition of claim 4, wherein said delivery agent is at least one of the following: amphiphilic molecule, lipid or polylysine.

7. The composition of claim 2, wherein said microsphere is crosslinked by a crosslinking agent.

8. **(Amended)** The composition of claim 7, wherein said crosslinking agent comprises a metal cation.

9. The composition of claim 8, wherein said metal cation comprises calcium.

10. The composition of claim 1, wherein said anionic molecule is alginate.

11. The composition of claim 1, wherein said cationic molecule is gelatin.

12. The composition of claim 1, wherein said cationic molecule is gelatin, and wherein said anionic molecule is alginate.

13. The composition of claim 4, wherein said transfer vector comprises at least one regulatory element.

14. The composition of claim 13, wherein said regulatory element is a promoter.

15. The composition of claim 4, wherein said transfer vector comprises an expression vector.

16. The composition of claim 4, wherein said transfer vector comprises a viral vector, said delivery agent is a virus, and said virus comprises at least about five percent by weight of said microsphere.

17. **(Amended)** The composition of claim 15, wherein said microsphere, when administered to a patient, provides controlled release of said expression vector.

18. The composition of claim 17, wherein said delivery agent facilitates intracellular delivery of said expression vector in said patient.

19. The composition of claim 18, wherein said expression vector produces a recombinant protein in said patient.

20. The composition of claim 19, wherein said recombinant protein is an antigen.

21. The composition of claim 4, wherein said microsphere is lyophilized.

22. The composition of claim 17, wherein said microsphere further comprises a second expression vector.

23. The composition of claim 1, wherein said nucleic acid is a viral vector, and said delivery agent is a virus.

24. **(Thrice Amended)** The composition of claim 2, wherein said delivery agent is a virus of [said] a viral vector.

25. The composition of claim 24, wherein said viral vector contains a transgene.

26. **(Amended)** The composition of claim 24, wherein said viral vector contains a nucleic acid encoding a recombinant gene product.

27. The composition of claim 26, wherein said gene product is an antigen.

28. The composition of claim 24, wherein said viral vector and said virus of said viral vector are one of the following: recombinant retrovirus, adenovirus, adeno-associated virus, or herpes simplex virus-1.

29. **(Twice Amended)** A gene delivery system for transducing cells, comprising: a coacervate microsphere encapsulating at least a nucleic acid and a delivery agent that is other than a cation of the coacervate, for facilitating intracellular delivery of said nucleic acid, wherein upon contact of cells with said coacervate microsphere, controlled release of said nucleic acid results in transduction of the cells by said nucleic acid.

30. **(Amended)** A method for delivering a nucleic acid into a cell, comprising: contacting a cell with a composition comprising a coacervate, wherein:

i. said coacervate incorporates a nucleic acid contained in a transfer vector having at least one regulatory element;

ii. said coacervate comprises a cationic molecule and an anionic molecule other than said nucleic acid;

iii. said coacervate is a microsphere; and,

iv. said coacervate incorporates a delivery agent,

wherein said contacting of a cell with said composition results in controlled release of said transfer vector in the cell.

31. The method of claim 30, wherein said transfer vector is a viral vector, said delivery agent is a virus of said viral vector, and said viral vector is enveloped in said virus.

32. **(Amended)** The method of claim 31, wherein the nucleic acid encodes a therapeutic agent, the [cells are] cell is in a host and [are] is transfected with the nucleic acid and [express] expresses the therapeutic agent, and said agent produces a therapeutically beneficial response in said host.

33. The method of claim 31, wherein said virus facilitates intracellular delivery of said viral vector.

34. **(Amended)** The method of claim 31, further comprising administering [to said host] said coacervate as a pharmaceutical composition to a host.

35. A kit containing a gene delivery system, comprising microspheres and instructions for using said microspheres, wherein said microspheres are comprised of a cationic molecule and an anionic molecule and said microspheres encapsulate a virus.

36. A coacervate microsphere for sustained release of a virus, comprising: a coacervate of gelatin and alginate having a virus incorporated therein.

37. **(Twice Amended)** The coacervate microsphere of claim 36, wherein said virus comprises a recombinant virus.

38. A method for the sustained release of a virus to a target site, comprising: providing to the target site a coacervate microsphere comprising a coacervate of gelatin and alginate having a virus incorporated therein.

39. A method for preparing a pharmaceutical preparation, comprising combining a pharmaceutically acceptable excipient with a coacervate of cationic and anionic molecules, wherein a recombinant virus is encapsulated in said coacervate.

40. A method for preparing a gene delivery system, comprising:

a. preparing a first solution of a cationic molecule and a second solution of an anionic molecule;

b. adding to either said first solution or said second solution a nucleic acid; and adding to either said first solution or said second solution a delivery agent;

c. combining said first solution and said second solution to form a third solution comprising the nucleic acid and the delivery agent; and,

d. isolating coacervates formed from a portion of said cationic molecule and a portion of said anionic molecule from said third solution,

wherein said coacervates encapsulate at least a portion of said nucleic acid and said delivery agent.

41. **(Amended)** The method of claim 40, wherein said coacervates consist essentially of microspheres.

42. **(Amended)** The method of claim 41, wherein said delivery agent comprises a virus particle including said nucleic acid.

43. The method of claim 41, further comprising mixing said third solution to form said coacervates.

44. The method of claim 42, wherein said first and said second solution are substantially aqueous.

45. The method of claim 42, further comprising preparing said microspheres for administration to a host, wherein preparing said microspheres does not impair the controlled release of said virus particle from said microspheres.

46. The method of claim 41, further comprising lyophilizing said microspheres after said isolation.

47. **(Amended)** A coacervate microsphere for transfection and expression of a recombinant protein prepared by the process comprising:

a. in any order:

i. adding a cationic molecule to a first aqueous solution;

ii. adding a anionic molecule to a second aqueous solution; and,

iii. adding to either said first or said second solution a virus comprising a viral vector comprising a nucleic acid encoding a recombinant protein and at least one regulatory element;

b. mixing said first and second solution together to form a coacervate microsphere of said cationic molecule and said anionic molecule encapsulating said virus; and,

c. isolating said coacervate microspheres,

wherein said coacervate releases said virus in vivo or in vitro, whereby said virus transfects cells, resulting in expression of said recombinant protein.

48. A gene delivery system for transfecting a cell with a viral vector, comprising:

a. encapsulation means for encapsulating a viral vector;

b. delivery means for facilitating intracellular delivery of said encapsulated viral vector;

wherein said encapsulation means comprises a coacervate, and wherein release of said encapsulated viral vector from said encapsulation means transfects a cell.

49. The composition of claim 1, wherein the nucleic acid encodes a polypeptide which inhibits cell proliferation.